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Br J Ophthalmol 2009 93: 594-596 originally published online December 19, 2008

doi: 10.1136/bjo.2008.149963

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The association between retinal vein ophthalmodynamometric force change and optic disc excavation

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Accepted 5 December 2008
Published Online First
19 December 2008

ABSTRACT

Aim: Retinal vein ophthalmodynamometric force (ODF) is predictive of future optic disc excavation in glaucoma, but it is not known if variation in ODF affects prognosis. We aimed to assess whether a change in ODF provides additional prognostic information.

Methods: 135 eyes of 75 patients with glaucoma or being glaucoma suspects had intraocular pressure (IOP), visual fields, stereo optic disc photography and ODF measured on an initial visit and a subsequent visit at mean 82 (SD 7.3) months later. Corneal thickness and blood pressure were recorded on the latter visit. When venous pulsation was spontaneous, the ODF was recorded as 0 g. Change in ODF was calculated. Flicker stereochronoscopy was used to determine the occurrence of optic disc excavation, which was modelled against the measured variables using multiple mixed effects logistic regression.

Results: Change in ODF ($p = 0.046$) was associated with increased excavation. Average IOP ($p = 0.66$) and other variables were not associated. Odds ratio for increased optic disc excavation of 1.045 per gram ODF change (95% CI 1.001 to 1.090) was calculated.

Conclusion: Change in retinal vein ODF may provide additional information to assist with glaucoma prognosis and implies a significant relationship between venous change and glaucoma patho-physiology.

Glaucoma is the second most common cause of blindness, with raised intraocular pressure (IOP) being the major treatable risk factor.^{1,2} Current techniques for monitoring glaucoma progression depend upon measuring the consequences of the disease, namely loss of neural tissue or visual field. Parameters that are associated with glaucoma progression risk are important to clinicians, as it provides valuable prognostic information before irreversible consequences of the disease have occurred. In a clinical setting, IOP and frequency of optic nerve haemorrhage are routinely used to determine glaucoma progression risk.^{2,3} We have recently shown that ophthalmodynamometric force (ODF) in retinal veins also has predictive value in determining the risk of glaucoma progression.⁴ A key question remains as to whether a change in ODF would provide additional prognostic information.

Ophthalmodynamometry is a simple clinical examination technique during which a force is applied to the globe while viewing vascular and other structures. Two to 10% of normal subjects have no spontaneous venous pulsation, whereas

46% of patients with glaucoma have no spontaneous venous pulsation.⁵⁻⁷ When spontaneous venous pulsation is not present, a force applied by an ophthalmodynamometer can be used to induce an increase in intraocular pressure leading to pulsation.^{5,6,8} This minimum force required to induce vein pulsation is termed the ophthalmodynamometric force. In this study retinal vein ODF measurements were repeated an average of 82 months after initial measurements, which have been previously reported.⁴ We studied the association between increased disc excavation and the change in ODF, as well as baseline ODF and other key parameters.

METHODS

Subjects

The same subjects described and used in our previous work provided data for this study.⁴ They were initially examined in 1996 and 1997, and invited back for re-examination in 2003. The research followed the tenets of the Declaration of Helsinki, in accordance with the University of Western Australia, Human Ethics Committee; all measurements and photography were taken after informed consent had been obtained from the subjects. Subjects were required to have clear ocular media and either have glaucoma with a repeatable Humphrey visual field full threshold defect and congruent optic disc excavation, or be a glaucoma suspect with either elevated intraocular pressure above 21 mm Hg or suspicious optic disc excavation. A total of 75 subjects with 135 eligible eyes were used. Of these eyes, 59 were glaucomatous with 55 suffering from primary open-angle glaucoma and four suffering from pigment dispersion associated with open-angle glaucoma. The remaining 76 eyes used in this study were glaucoma suspects.

Data collection and experimental procedure

At the initial visit, intraocular pressure was measured with Goldmann applanation tonometry, and then the pupils were dilated, allowing simultaneous stereo disc photography (Nidek 3DX, Gamagori, Japan). Central and hemiretinal veins were examined for the presence of pulsation. If absent, a contact lens ophthalmodynamometer (American Optical, Buffalo, New York)⁹ was used to measure the minimum ODF required to induce a segment of vein pulsation. If spontaneous venous pulsation was present, then the ODF was said to

be 0. A Humphrey (Humphrey Systems, Dublin, California) 24-2 visual field test was also performed on the initial visit. The Humphrey full threshold visual field from a second or later examination within 3 months of examination was also used to provide the mean deviation. The presence (1) or absence (0) of an optic nerve haemorrhage (ONH) was also recorded as a binary value on the initial visit.

At the final visit, intraocular pressure measurement, central corneal thickness measurement (Quantel, Pocket Pach 2, Clemont, France), blood pressure, stereo disc photography and observation of retinal vein pulsation with ODF measurement were performed. Between the initial and final examination, the patients were treated at their ophthalmologist's discretion. Time integrated IOP was calculated using the sum of the mean IOP at each eye clinic visit interval multiplied by the length of each interval, then divided by the interval between the initial and final visits. The standard deviation of all IOP measurements from each individual eye was also calculated.

Simultaneous stereo disc photographs from all eyes were compared as described previously using stereo flicker chronoscopy.^{4 10} Three independent observers examined all stereo disc photographs and were blinded to the identity of the photographs. Each observer examined optic discs for the presence or absence of a disc rim haemorrhage and for loss of neuroretinal rim. The location of the neuroretinal rim change was documented as being the nasal, superior, temporal or inferior quadrants. Increased excavation (recorded as a binary yes (1) or no (0) variable) was said to occur when all three observers noted loss of neuroretinal rim in the same location. Where one or two out of the three observers noted a change, the stereo photographs were reviewed together at a consensus meeting and a decision made as to whether a change had occurred. Similarly, ONH was said to occur when all three observers agreed or when consensus was reached regarding observation of the initial disc photographs. The change in ODF (Δ ODF) was calculated by subtracting the initial ODF from the final ODF for each eye. The mean ODF was calculated also. The mean blood pressure was calculated as diastolic+(systolic-diastolic)/3.

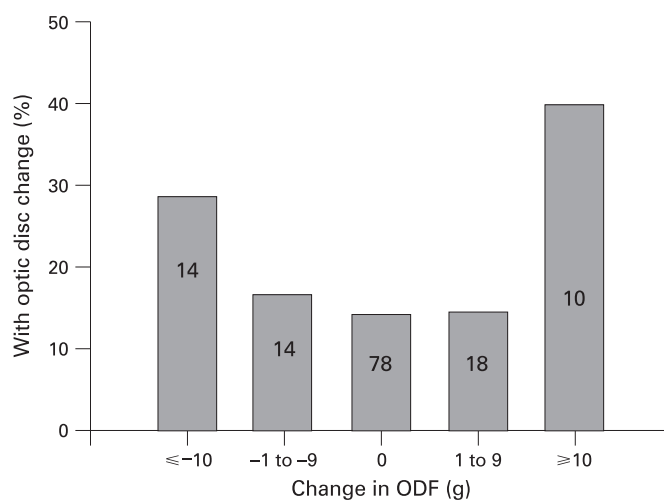


Figure 1 Graph showing percentage of eyes that demonstrated increased optic disc excavation at the various levels of change in retinal vein ophthalmodynamometric force (ODF). The change in ODF is the final ODF minus initial ODF. The numbers in each bar are the numbers of eyes in each ODF change level.

Statistical analysis

The mean and standard deviations were calculated and reported as well as results using the Student *t* test to compare means. We modelled the probability of increased disc excavation as a function of time integrated IOP, IOP standard deviation, initial ODF, Δ ODF, initial mean deviation, central corneal thickness, mean blood pressure, pulse blood pressure, age and sex. The presence of optic disc rim haemorrhage could not be included in the model because there were too few eyes with haemorrhage to derive a numerically stable fitted model when Δ ODF was also present. This analysis employed data from both eyes through a generalised linear mixed model with logit link function and a normal random effect to account for intereye correlation within subjects (ie, a mixed effects logistic regression), as described previously.^{4 5 11 12} We also considered interaction terms between the binary variables (ONH and sex) and the quantitative explanatory variables. Backwards variable selection was implemented using Wald *t* tests, with $p > 0.1$ as a criterion for variable removal. All calculations were performed using the statistical software package R.¹³

RESULTS

Data from 135 eyes of 75 subjects were analysed with a mean initial to final visit interval of 82 (SD 7.3) months. One eye was excluded from the previously published data set because no ODF could be recorded at the final visit.⁴ The Mean age was 68 (12.2) years with 36 women and 39 men, and with no significant sex difference between age, MD, CCT, exam interval or the proportions that progressed. Of the glaucoma suspects, 42% were female, with a mean age of 65.6 years, being not significantly younger than the glaucoma group with 55% females and a mean age of 69.6 years ($p = 0.052$). Forty-three subjects had no spontaneous venous pulsation at the initial visit, with a mean ODF of 12.3 (11.0) g (range 1 to 50 g) equivalent to 0.121 Newton force. The change in ODF ranged from -32 to 76 g, with 28 eyes having a change of < 0 g and 28 having a change of > 0 g. Thirty-five per cent of the 23 eyes without spontaneous venous pulsation at both visits progressed, whereas 14% of the 77 eyes with spontaneous venous pulsation at both visits progressed. Of the 93 eyes with spontaneous venous pulsation at the initial visit, 16 had absent spontaneous venous pulsation at the final visit. Two of these 16 eyes progressed (12.5%), but only three of these 16 eyes had ODF values greater than 10 g at the final visit. Twenty-six per cent of 39 eyes with no spontaneous venous pulsation at the final visit progressed, whereas 15% of 96 eyes with spontaneous venous pulsation at the final visit progressed. The mean time integrated IOP was not significantly different ($p = 0.66$) between eyes that progressed (17.3 (3.4) mm Hg) and those that did not (17.6 (3.6) mm Hg).

The variable selection procedure for the mixed effects logistic regression terminated when only Δ ODF remained in the model. This variable was significantly associated with increased optic disc excavation ($p = 0.046$, coefficient 0.044, SE 0.022). Initial ODF and final ODF both have a statistically significant impact on the probability of disc excavation ($p = 0.026$ and $p = 0.031$ respectively) when modelled in the absence of all other variables. There was significant interdependence between the ODF variables with final ODF and Δ ODF having a correlation coefficient of 0.823 ($p = 0.000$). Based on our fitted model, the odds ratio for increased disc excavation rises by a factor of 1.045 per gram change in ODF (95% CI 1.001 to 1.090). The relationship between Δ ODF and disc excavation is shown in fig 1, with 14% of eyes having 0 g Δ ODF progressing and 40% of

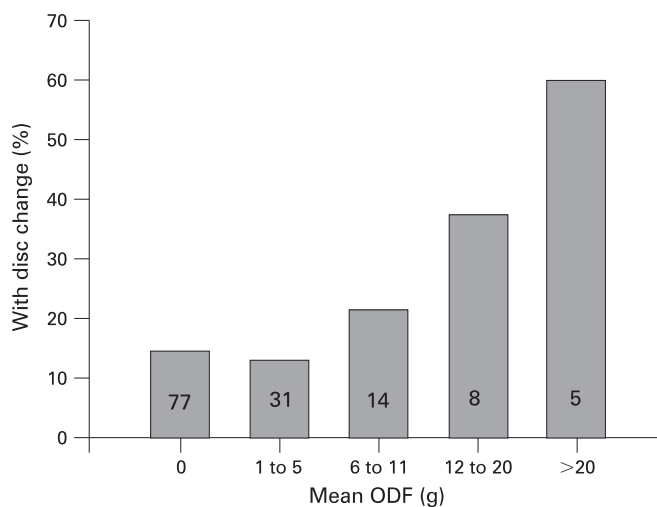


Figure 2 Graph showing the percentage of eyes that demonstrated increased optic disc excavation at the various levels of mean retinal vein ophthalmodynamometric force (ODF). The mean ODF is the average of initial ODF and final ODF. The numbers in each bar are the numbers of eyes in each ODF change level.

eyes with change in ODF ≥ 10 g showing increased disc excavation. Twenty-eight per cent of eyes with a change in ODF of ≤ -10 g progressed, but it should be noted that 12 out of the 14 eyes with a change in ODF of ≤ -10 g had an initial ODF of ≥ 15 g. The chance of increased disc excavation increased with mean ODF, such that 60% with a mean ODF of >20 g showed an increased excavation (fig 2).

DISCUSSION

This work demonstrates that the change in retinal vein ODF is significantly associated with an increased chance of optic disc excavation. An increase in ODF appears to indicate an increased risk and a worsening of glaucoma. Using the odds ratio of 1.045 per gram ODF and previously published pig calibration data, this is equivalent to an odds ratio for increased disc excavation of 1.062 per mm Hg increase in vein pulsation pressure.^{5 14} To date, all methods of monitoring response to glaucoma treatment have depended upon measuring increased optic nerve damage. In addition to IOP, central corneal thickness, age, visual field and optic disc parameters,¹⁵ the change in ODF may add to the information which clinicians find useful for determining progression risk in their patients.

A significant relationship may exist between retinal vein changes and glaucoma. The exact nature of this change is unknown and could reflect the influences upon flow within and compressive forces external to the retinal veins.^{5 16 17} These putative factors have been extensively discussed in prior work, with retinal venous narrowing being the most plausible explanatory factor.^{4 5 16 18} Glaucoma patients are at increased risk of central¹⁹ and hemiretinal²⁰ vein occlusion, and the causation of optic nerve haemorrhages may involve a pathological venous component.²¹ The patho-physiological cause of the greater ODF required for venous pulsation in glaucoma is not

known with certainty, although it may involve narrowing of the central and hemiretinal veins.¹⁶ Our results suggest that venous alterations occur in glaucoma. These alterations are associated with and may play a causative role in optic nerve neural tissue loss.

The change in retinal vein ophthalmodynamometric force required to induce pulsation appears to be significantly associated with optic disc excavation and may be a useful new indicator of progression risk. An increase in ODF appears to be a sign indicative of increased risk. A further study is warranted to clarify the relative significance of changes in ODF in relation to other risk factors.

Funding: The McCusker Glaucoma Centre, and National Health and Medical Research Council program grant 211901 provided financial support.

Competing interests: None.

Ethics approval: Ethics approval was provided by the University of Western Australia, Human Ethics Committee.

Patient consent: Obtained.

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2008-12-19

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